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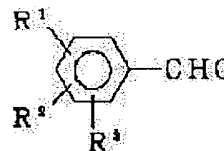
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(54) PRODUCTION OF MANDELIC ACID DERIVATIVE

(57)Abstract:

PROBLEM TO BE SOLVED: To safely obtain the subject compound in a high yield and in a high purity in one process by dropping an acid to an aldehyde derivative in the presence of a cyano compound and subsequently hydrolyzing the reaction product with a mineral acid.

SOLUTION: This method for producing a mandelic acid derivative comprises dropping an acid (A) to an aldehyde derivative of the formula (R¹-R³ are each H, a halogen, a 1-5C alkyl, a 1-5C alkoxy, hydroxyl group, phenyl which may be substituted) in the presence of (B) a cyano compound in a solvent and subsequently hydrolyzing the obtained corresponding mandelonitrile derivative with a mineral acid. The solvent is especially preferably ethyl acetate, and is used in an amount of 0.5-5 weight times that of the component A. The component B includes sodium cyanate and potassium cyanate, and is used in an amount of 1-4 moles, preferably 1.1-1.3 moles, per mole of the component A. Thereby, the mandelic acid derivative useful as a synthetic intermediate for medicines can safely be obtained in a high yield and in a high purity in only one process.



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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to the manufacture approach of a mandelic acid derivative. The mandelic acid derivative is useful as synthetic intermediate field of drugs.

[0002]

[Description of the Prior Art] The various manufacture approaches are proposed by the mandelic acid derivative from before. As a typical thing, Org.Synth., Coll.Vol., I, 336 (approach 1 (1941)), Org.Synth., Coll.Vol., III, 538 (approach 2 (1955)), A.Merz, Synthesis, and the approach indicated by 724 (approach 3 (1974)) are learned. However, although an approach 1 has many routing counters and is complicated, a process is complicated although an approach 2 uses a cheap raw material, the purity of a product is low and the process of an approach 3 is short, there are troubles, like yield is low and an odor is excessive. [of routing counters] Although approaches other than these are also learned, there is same trouble, and neither can say it as an advantageous approach industrially.

[0003]

[Problem(s) to be Solved by the Invention] Therefore, the purpose of this invention is to offer the manufacture approach of an advantageous mandelic acid derivative simple and industrially.

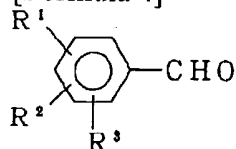
[0004]

[Means for Solving the Problem] Then, it found out that it hydrolyzed by the mineral acid, without making hydrogen cyanide add to an aldehyde derivative by dropping the bottom of existence of cyanides, and an acid at an aldehyde derivative as a result of inquiring wholeheartedly that this invention persons should solve said technical problem, considering as a MANDERO nitril derivative, and isolating this, and was only 1 process from an aldehyde derivative, and a mandelic acid derivative could moreover be safely manufactured by high yield and the high grade. Even if it permuted like 4-phenyl mandelic acid especially by the phenyl group made low [yield and purity] in the conventional method, they were high yield and a high grade very much. This invention comes to be completed based on this discovery.

[0005] Namely, summary of this invention (1) General formula (I)

[0006]

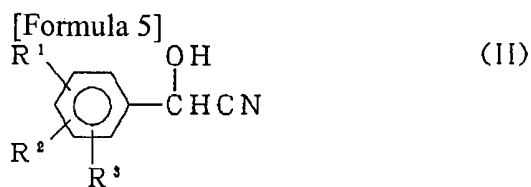
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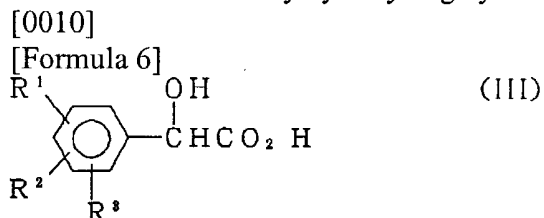
(I)

[0007] (-- among a formula, it may be different from each other and R1, R2, and R3 express the same or the phenyl group which may have a hydrogen atom, a halogen atom, the alkyl group of carbon numbers 1-5, the alkoxy group of carbon numbers 1-5, a hydroxyl group, or a substituent, respectively.) -- the aldehyde derivative shown -- the bottom of existence of cyanides, and the inside of a solvent -- an acid -- being dropped -- general formula (II)

[0008]



[0009] (-- R₁, R₂, and R₃ express the respectively same semantics as R₁ in a general formula (I), R₂, and R₃ among a formula.) -- general formula (III) which considers as the MANDERO nitril derivative shown and is characterized by hydrolyzing by the mineral acid, without isolating this



[0011] R₁ [3 / inside of formula, R₁, R₂, and / R] in a general formula (I) -- R₂ And the respectively same semantics as R₃ is expressed. The manufacture approach of the mandelic acid derivative shown (2) A solvent Ethyl acetate, Organic solvents, such as toluene, a tetrahydrofuran, an acetic acid, a methanol, ethanol, and propanol, The manufacture approach of the aforementioned (1) publication characterized by being water or those mixed solvents, (3) The above (1) characterized by heating and distilling off a solvent in case it hydrolyzes, or the manufacture approach given in (2) (4) With the mineral acid added in case it hydrolyzes aforementioned (1) - (3) characterized by adding an acetic acid -- either -- the manufacture approach of a publication, and a list -- (5) aforementioned (1) - (4) characterized by the mandelic acid derivative shown by the general formula (III) being 4-phenyl mandelic acid -- either -- it is related with the manufacture approach of a publication.

[0012]

[Embodiment of the Invention] Below, this invention is explained at a detail. The MANDERO nitril derivative which the aldehyde derivative first shown by the general formula (I) is made to add hydrogen cyanide to an aldehyde derivative, and is shown in it by the general formula (II) by dropping an acid under existence of cyanides and in a solvent is made to generate in this invention.

[0013] Although the approach of trickling a cyanides water solution and an acid, respectively, the approach of trickling an acid into the aldehyde derivative in a solvent and cyanides, etc. are mentioned to the aldehyde derivative in a solvent as the process, in this invention, the approach of trickling an acid into the aldehyde derivative and cyanides in a solvent is desirable.

[0014] The aldehyde derivative used as the raw material of this invention is shown by the general formula (I). The inside of a formula, R₁, and R₂ And R₃ It may be different from each other and the same or the phenyl group which may have a hydrogen atom, a halogen atom, the alkyl group of carbon numbers 1-5, the alkoxy group of carbon numbers 1-5, a hydroxyl group, or a substituent, respectively is expressed. As an alkyl group of carbon numbers 1-5, a methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, sec-butyl, tert-butyl, a pentyl radical, etc. can be illustrated. As an alkoxy group of carbon numbers 1-5, a methoxy group, an ethoxy radical, a propoxy group, an isopropoxy group, a butoxy radical, an iso butoxy radical, a sec-butoxy radical, a tert-butoxy radical, a pentyloxy radical, etc. can be illustrated. As a substituent which may be permuted by the phenyl group, a halogen atom, the alkyl group of carbon numbers 1-5, the alkoxy group of carbon numbers 1-5, a hydroxyl group, etc. can be illustrated.

[0015] Specifically, a benzaldehyde, 4-fluoro benzaldehyde, 4-chlorobenzaldehyde, 4-BUROMO benzaldehyde, 4-methyl benzaldehyde, 4-ethyl benzaldehyde, 4-propyl benzaldehyde, 4-butyl benzaldehyde, 4-pentyl benzaldehyde, 4-methoxy benzaldehyde, a 4-ethoxy benzaldehyde, a 4-propoxy benzaldehyde, a 4-butoxy benzaldehyde, a 4-pentyloxy benzaldehyde, a 4-hydroxy benzaldehyde, 4-phenyl

benzaldehyde, etc. can be illustrated. These can use a commercial item as it is.

[0016] As a solvent used in this invention, although organic solvents, such as ethyl acetate, toluene, a tetrahydrofuran, an acetic acid, a methanol, ethanol, and propanol, water, or those mixed solvents are used, especially ethyl acetate is desirable. Moreover, the amount used has desirable 0.5 - 5 weight twice to an aldehyde derivative.

[0017] A sodium cyanide, a potassium cyanide, etc. are raised as cyanides used for this invention. Moreover, the amount used has preferably desirable 1.1-1.3 mols 1-4 mols to one mol of aldehyde derivatives.

[0018] As an acid used for this invention, although organic acids, such as mineral acids, such as a hydrochloric acid and a sulfuric acid, and methansulfonic acid, etc. are used, a mineral acid is desirable and a hydrochloric acid is used suitably even especially in inside. Moreover, the amount used has desirable 1-3 mols to one mol of aldehyde derivatives.

[0019] Reaction temperature is usually 0-30 degrees C, and although a short time is sufficient since the unreacted object of an aldehyde derivative hardly remains if reaction time finishes trickling an acid, it is desirable that an acid is usually dropped over 30 minutes - 4 hours.

[0020] Thus, the obtained MANDERO nitril derivative is shown by the general formula (II). The inside of a formula, R1, and R2 And R3 R1 in a general formula (I), and R2 And the respectively same semantics as R3 is expressed. Specifically MANDERO nitril, 4-fluoro MANDERO nitril, 4-clo romantic DERONI tolyl, 4-BUROMOMANDERO nitril, 4-methyl MANDERO nitril, 4-ethyl MANDERO nitril, 4-propyl MANDERO nitril, 4-butyl MANDERO nitril, 4-pentyl MANDERO nitril, 4-methoxy MANDERO nitril, 4-ethoxy MANDERO nitril, 4-propoxy MANDERO nitril, 4-butoxy MANDERO nitril, 4-pentyloxy MANDERO nitril, 4-hydroxy MANDERO nitril, 4-phenyl MANDERO nitril, etc. can be illustrated.

[0021] Since hydrogen cyanide with it remains, let the MANDERO nitril derivative shown by the generated general formula (II) be the mandelic acid derivative which is made to hydrolyze under existence of an acetic acid further with a mineral-acid independent or a mineral acid, and is shown by the general formula (III) by this invention, without isolating this. [bad and stability and] [unreacted]

[0022] By this, since a mineral acid etc. is added as it is and it is made to hydrolyze, without isolating the MANDERO nitril object which uses within a well-closed container and is generated although cyanides is used in this invention, the mandelic acid derivative shown in insurance by the general formula (III) can be obtained.

[0023] Hydrolysis usually adds a mineral acid at the temperature of 0-30 degrees C, and is performed by heating at 50-110 degrees C after that. Although reaction time changes with reaction temperature, it is usually about 2 - 10 hours. In this invention, a solvent may be distilled off in the case of heating.

[0024] As a mineral acid for hydrolysis, although a hydrochloric acid, a sulfuric acid, etc. are mentioned, especially a hydrochloric acid is desirable. Moreover, especially the amount used has desirable 2-8 mols 1-15 mols to one mol of aldehyde derivatives. In this invention, hydrolysis can be promoted by adding a meltable acetic acid to both of organic solvents, such as water and ethyl acetate, further. The amount used has desirable 1 - 3 weight twice to an aldehyde derivative.

[0025] The generated mandelic acid derivative is taken out by normal operation, such as filtration, washing, an extract with an organic solvent, and crystallization.

[0026] Thus, the mandelic acid derivative obtained is shown by the general formula (III). The inside of a formula, R1, and R2 And R3 R1 in a general formula (I), and R2 And R3 The respectively same semantics is expressed. Specifically, mandelic acid, 4-fluoro mandelic acid, 4-chloro mandelic acid, 4-BUROMO mandelic acid, 4-methyl mandelic acid, 4-ethyl mandelic acid, 4-propyl mandelic acid, 4-butyl mandelic acid, 4-pentyl mandelic acid, 4-methoxy mandelic acid, 4-ethoxy mandelic acid, 4-propoxy mandelic acid, 4-butoxy mandelic acid, 4-pentyloxy mandelic acid, 4-hydroxy mandelic acid, 4-phenyl mandelic acid, etc. can be illustrated. The mandelic acid derivative obtained by the manufacture approach of this invention is useful as synthetic intermediate field of drugs.

[0027]

[Example] Hereafter, although an example explains this invention in more detail, this invention is not

limited at all by these examples.

[0028] 20ml (18g) of ethyl acetate, 4-phenyl benzaldehyde 10g (55 millimol), and 4g (61.4 millimol) of potassium cyanides were taught to 1100ml flask of examples, and 6.3g (60.5 millimol) of concentrated hydrochloric acid was dropped over 70 minutes at 15-20 degrees C. After agitating at this temperature for 1 hour, 60g (0.58 mols) of concentrated hydrochloric acid was dropped, it heated at 85-90 degrees C, and ethyl acetate was distilled off. It heated for 2 hours, it cooled to the room temperature, and 12g 4-phenyl mandelic acid was obtained filtration, backwashing by water, and by drying. (96.1% of yield, HPLC purity = 96%)

Elemental-analysis actual measurement Carbon 73.4% Hydrogen 5.5% Calculated value (C₁₄H₁₂O₃)

Carbon 73.4% Hydrogen 5.3% [0029] 20ml (18g) of ethyl acetate, 4-phenyl benzaldehyde 10g (55 millimol), and 4g (61.4 millimol) of potassium cyanides were taught to 2100ml flask of examples, and 6.3g (60.5 millimol) of concentrated hydrochloric acid was dropped over 45 minutes at 10-15 degrees C. Subsequently, 45ml (0.25 mols) of hydrochloric-acid water solutions was poured in 20% of the weight, it heated at 85-90 degrees C, and ethyl acetate was distilled off. It heated at 85 degrees C for 2 hours, it cooled to the room temperature, and 12.2g 4-phenyl mandelic acid was obtained filtration, backwashing by water, and by drying. (96.5% of yield, HPLC purity = 95.1%)

[0030] Toluene 10ml (8.7g) and 4-phenyl benzaldehyde 10g (55 millimol) were taught to 3100ml flask of examples, and, subsequently 11.4ml (0.13 mols) of concentrated hydrochloric acid was first dropped for the liquid which dissolved 5.4g (83 millimol) of potassium cyanides in 10ml of water at 15-20 degrees C over 90 minutes, respectively. 60ml (0.69 mols) of concentrated hydrochloric acid was poured in, and it heated at 75-80 degrees C, and agitated for 5 hours. It cooled to the room temperature and 12.4g 4-phenyl mandelic acid was obtained filtration, backwashing by water, and by drying. (99.3% of yield, HPLC purity = 93.5%)

[0031] 400ml (360g) of ethyl acetate, 4-phenyl benzaldehyde 200g (1.098 mols), and 86g (1.32 mols) of potassium cyanides were taught to the example 42L flask, and 137g (1.32 mols) of concentrated hydrochloric acid was dropped over 3 hours at 20-25 degrees C. 1132ml (6.2 mols) of hydrochloric-acid water solutions was poured in 20% of the weight after 2-hour stirring, it heated at 90-95 degrees C, and ethyl acetate was distilled off. It heated at 95-100 degrees C for 5 hours, it cooled to the room temperature, and 250g 4-phenyl mandelic acid was obtained filtration, backwashing by water, and by drying. (99.9% of yield, HPLC purity = 99.2%)

[0032] 1200ml (1080g) of example 5 ethyl acetate, 4-phenyl benzaldehyde 600g (3.29 mols), and 258g (3.96 mols) of potassium cyanides were prepared, and 413g (3.96 mols) of concentrated hydrochloric acid was dropped over 3 hours at 16-26 degrees C. 1200ml (1080g) of acetic acids and 810ml (9.3 mols) of concentrated hydrochloric acid were poured in after 2-hour stirring, it heated at 90-100 degrees C, and ethyl acetate was distilled off. 1500ml of water was added, and it heated at 98-106 degrees C for 5 hours, it cooled to the room temperature, and 725g 4-phenyl mandelic acid was obtained filtration, backwashing by water, and by drying. (96.5% of yield, HPLC purity = 99%)

[0033] 20ml (20g) of example 6 water, the liquid which dissolved 7.2g (0.198 mols) of potassium cyanides in 20ml of water at 4-phenyl benzaldehyde 10g (55 millimol) slurry liquid, and 11.4g (0.11 mols) of concentrated hydrochloric acid were dropped over 2 hours at 8-15 degrees C. Subsequently, 60ml (0.69 mols) of concentrated hydrochloric acid was poured in, and it heated at 68-70 degrees C for 10 hours. It cooled to the room temperature and 6.12g 4-phenyl mandelic acid was obtained filtration, backwashing by water, and by drying. (96.7% of yield, HPLC purity = 96%)

[0034] After adding 4-phenyl benzaldehyde 600g (3.29 mols) to 1200ml (1080g) of example 7 ethyl acetate and dissolving in it, the liquid which dissolved 258g (3.95 mols) of potassium cyanides in 720ml of water was added, and it cooled at about 15 degrees C. Subsequently, 413g (3.95 mols) of concentrated hydrochloric acid was dropped over 3 hours at 10-30 degrees C, and it stirred for 1 hour. After having poured in 1258g of acetic acids, and 948g (9.08 mols) of concentrated hydrochloric acid, heating at 85-90 degrees C and flowing back for 5 hours, ethyl acetate was distilled off at 90-100 degrees C, 780g of water was added, and the temperature up was carried out to 105 more degrees C. After 2-hour stirring, it cooled

to the room temperature and 724g 4-phenyl mandelic acid was obtained filtration, backwashing by water, and by drying. (96.3% of yield, HPLC purity = 99.3%)

[0035] Example 84-phenyl benzaldehyde 100g (0.549 mols) was dissolved in 200ml (180g) of ethyl acetate, and 43g (0.66 mols) of potassium cyanides was mixed with the liquid which dissolved in 120ml of water. Subsequently, 72.6g (0.7 mols) of concentrated hydrochloric acid was dropped over 2 hours at 15-25 degrees C, and it stirred for 1 hour. After having poured in 215g of acetic acids, and 360g (3.5 mols) of concentrated hydrochloric acid, heating at 80-85 degrees C and flowing back for 4 hours, ethyl acetate was distilled off at 85-95 degrees C, and it cooled at 25 degrees C. 120.7g 4-phenyl mandelic acid was obtained for the crystal which carried out crystallization filtration, backwashing by water, and by drying. (96.4% of yield, HPLC purity = 98.6%)

[0036]

[Effect of the Invention] It is high yield and a high grade, and the manufacture approach of this invention enabled it to obtain a mandelic acid derivative safely.

[Translation done.]